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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,601	STRITTMATTER, STEPHEN M.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-11,13,17 and 21-32* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,6-11,13,17,21-30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1,2,6-11,13,17 and 21-32* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *13 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-4-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 11-24-03, supplemental to the non-compliant amendment of 10-17-03, has been entered into the record and has been fully considered.

2. Newly submitted claim 31 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 31 is directed to a method for inhibiting a rho or rac dependent kinase activity. The method is patentably distinct in that the claim recites a unique method with different effects, functions, and steps and utilizes distinct reagents. Thus the method is patentably distinct and separable. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 31 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections

3. Claim 1 and 32 are objected to because of the following informalities: Claim 1a) recites rho in duplicate where the claim is apparently intended to recite rho or rac protein. Claim 32 is missing the apparent article "and" prior to an associated kinase. Appropriate correction is required.

Specification

4. 37CFR § 1.71 Detailed description and specification of the invention.

(a) The specification must include a written description of the invention or discovery and of the manner and process of making and using the same, and is

required to be in such full, clear, concise, and exact terms as to enable any person skilled in the art or science to which the invention or discovery appertains, or with which it is most nearly connected, to make and use the same.

(b) The specification must set forth the precise invention for which a patent is solicited, in such manner as to distinguish it from other inventions and from what is old. It must describe completely a specific embodiment of the process, machine, manufacture, composition of matter or improvement invented, and must explain the mode of operation or principle whenever applicable. The best mode contemplated by the inventor of carrying out his invention must be set forth.

5. The disclosure is objected to under 37 CFR 1.71, as being so incomprehensible as to preclude a reasonable search of the prior art by the examiner. For example, the following items are not understood: Applicants claims are newly directed to administration of a composition containing as follows: 1) ribosylating compounds capable of ADP-ribosylating rho protein, 2) ribosylating compounds capable of ADP-ribosylating rac protein), 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity. While such compounds appear

to be alleged rho or rac inhibitors, the specification provides no guidance as to the particular structures and/or their correlating functions as encompassed by the various functional claim recitations.

Applicants are required to clarify the disclosure so that the examiner may make a proper comparison of the newly claimed invention (compositions) within the prior art.

Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

A preliminary examination of this application reveals that this new functional terminology is so different from that which is generally accepted in the art to which this invention pertains that a proper search of the prior art cannot be made. For example: there appears to be no disclosure or art related to any class of molecules known to exhibit the noted functional activities now claimed and it is further unclear how such recitations relate to the previous claim language directed to either rho or rac inhibitors. The new claims and specification fail to disclose any correlating structure such that the artisan or Examiner could perform any meaningful search of known prior art compounds that are either rho or rac inhibitiors and are known to function via the mechanisms (functional language) recited.

Applicant is required to provide a clarification of these matters or correlation with art-accepted terminology so that a proper comparison with the prior art can be made. Applicant should be careful not to introduce any new matter into the disclosure (i.e., matter which is not supported by the disclosure as originally filed).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 6-11, 13, 17, 21-27 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The newly presented claims are drawn to administration as follows: 1) ribosylating compounds capable of ADP-ribosylating rho protein, 2) ribosylating compounds capable of ADP-ribosylating rac protein), 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity.

Applicants point to support for such amendments within the specification at p. 4, lines 7-9 and p. 10, lines 11-17. In particular p. 4 notes that C3 transferase (exoenzyme) ADP ribosylates rho specifically and inactivates the G protein. However,

such does not speak to support for 2) ribosylating compounds capable of ADP-robosylating rac protein as claimed. In addition, p. 10, lines 10-17 notes various interpretations of a "rho protein inhibitor". However the recitations of the claims do not readily flow from these descriptions. In particuar, there is no discussion of 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity. Support is not further found for the particular recitations of the dependent claims as directed to compositions comprising rho protein, rac protein, C. botulinum C3 inhibitor, inhibition of a rac protein, inhibition of a rho protein, inhibition of both a rac and rho protein, and to an antibody directed against rho, rac and an associated kinase. Thus, the recitations constitute new matter absent particular notation for their support.

8. Claims 1-2, 6-11, 13, 17, 21-23, 28-30 and 32 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification describes the polypeptide of C. botulinum C3 transferase (exoenzyme) which has been shown to exhibit ADP-ribosylating activity specifically to rho protein. However, the claims as written include any compound capable of exhibiting the following noted activities, 1) ribosylating compounds capable of ADP-ribosylating rho protein, 2) ribosylating compounds capable of ADP-ribosylating rac protein, 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity. As recited, the claims encompass any compound capable of meeting the noted functional activities where only C3 exoenzyme is noted to ADP-ribosylate rho, the function noted in 1) above. No other compounds which exhibit the function of 1) above are noted and further no structures achieving the functaional activities of elements 2)-7) above are described. The instant disclosure of a single polypeptide, that of C. botulinum C3 exoenzyme, with the instantly disclosed specific activity of ADP-ribosylating rho, does not adequately support the scope of the genus or subgenric recitation of 1) ribosylating compounds capable of ADP-ribosylating rho protein as claimed, which encompasses a substantial variety of subgenera. Moreover a lack of any adequate structure noted to elicit the functional activities of elements 2-7

clearly fails to support the scope of a genus or subgeneric recitation.

A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Id at 1170, 25 USPQ2d at 1606."

A description of a genus may be achieved by means of a recitation of a representative number of members, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

The instant specification discloses, however, a single isolated polypeptide capable of stimulating ADP-ribosylation of rho, and no other compounds proposed to possess the same activities as that of the claims. The specification fails to note a single exemplary compound which is capable of providing for; 2) ribosylating compounds capable of ADP-ribosylating rac protein), 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity. No structure is set forth for the additional activities. Thus, the specification lacks adequate written description support for the claimed invention.

9. Claims 1-2, 6-11, 13, 17, 21-30 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro stimulation of axon outgrowth with C. botulinum C3 exoenzyme, does not reasonably provide

enablement for in vivo promotion of CNS axon growth with ribosylating compounds capable of ADP-ribosylating rho or rac protein, at least one blocking compound capable of physically interacting with rho or rac or an associated kinase and inhibiting complex formation or at least one inhibiting compound capable of physically interacting with a complex comprising rho or rac and an associated kinase and inhibiting the kinase activity of said complex as newly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The previous enablement rejection of 8-13-01 is noted and is maintained herein as previously set forth. However, the rejection is reiterated as a scope of enablement rejection to highlight the issues. The issues are whether or not the specification enables the broad scope of the claims. It was previously noted and is reiterated that the specification is enabling for the in vitro promotion of CNS axon outgrowth (via DRG neurons) using C. botulinum C3 exoenzyme. However, it is not agreed that Applicant's specification is enabling to the claimed methods with respect to the in vivo promotion of CNS axon outgrowth in a patient with either C. botulinum C3 exoenzyme or the broad scope of the claims as directed to compositions containing 1) ribosylating compounds capable of ADP-ribosylating rho protein, 2) ribosylating compounds capable of ADP-ribosylating rac protein, 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6)

at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity.

The previous rejection is further reiterated with respect to the specification's lack of working embodiments in an art accepted model of in vivo CNS axonal outgrowth and the unpredictability associated with extrapolation of in vitro findings to the in vivo CNS situation. Bartsch et al., previously of record is noted with respect to teaching the necessity to test and confirm in vitro findings in vivo with respect to the CNS. Lehman et al., previously of record is noted with respect to post-filing date evidence (9-1-99) of C3 exoenzyme induced optic nerve outgrowth (regeneration) following optic nerve crush.

The specification at pp. 16, lines 12-16 notes that C. botulinum C3 exoenzyme was the only protein altering rho activity that altered dorsal root ganglia outgrowth in culture. The treated neurites were observed to double their outgrowth or extension following treatment. Page 18, lines 3-13 note the specificity of C3 action in inhibition of rho activity through ADP-ribosylation and pp. 23, line 20-pp. 24, line 3 teach a C3 expressing adenovirus vector that was able to infect neurons both in vitro and in vivo as measured by EGFP expression. While it was noted that the C3 virus infected in vitro cultures were rendered insensitive to semD and myelin, the specification is silent as to any effect in promoting CNS axon outgrowth either in vitro or in vivo using the adenovirus C3 construct. Thus, there is no exemplification or enablement for a method

for promoting CNS axon growth in a patient (in vivo) as claimed. Moreover, C. botulinum C3 exoenzyme is the only rho inhibitor noted that effects axonal growth by promoting neurite extension and the finding is only exemplified in vitro.

In addition, the specification fails to teach compounds other than C. botulinum C3 exoenzyme that are effective to promote neurite outgrowth. While the specification notes that C3 exoenzyme from C. botulinum ADP- ribosylates rho specifically and inactivates this G protein, the specification is silent as to compounds that are; ribosylating compounds capable of ADP-ribosylating rac protein, a blocking compound capable of physically interacting with rho and inhibiting complex formation, a blocking compound capable of physically interacting with rac and inhibiting complex formation, a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity. Thus, the disclosure of C3 exoenzyme activity in ADP-ribosylating rho is not commensurate in scope with the compounds and requisite activities instantly claimed.

The claims are akin to a single means claim, i.e., where a means recitation does not appear in combination with another recited element of means and is subject to an undue breadth rejection under 35 USC 112, first paragraph because the specification at most would only disclose those means known to the inventor at the time of the invention, see in particular MPEP 2164.08(a). As noted only a single peptide

compound is noted to provide the activity of 1) ribosylating compounds capable of ADP-ribosylating rho protein, while no structures are noted to provide for; 2) ribosylating compounds capable of ADP-ribosylating rac protein, 3) a blocking compound capable of physically interacting with rho and inhibiting complex formation, 4) a blocking compound capable of physically interacting with rac and inhibiting complex formation, 5) a blocking compound capable of physically interacting with an associated kinase and inhibiting complex formation, 6) at least one inhibiting compound capable of physically interacting with a complex comprising rho and an associated kinase and inhibiting kinase activity, and 7) at least one inhibiting compound capable of physically interacting with a complex comprising rac and an associated kinase and inhibiting kinase activity.

Applicants argue in the response of 2-13-02 that a declaration by Dr. Strittmatter presented the same date points out that, "investigators in the field routinely employ in vitro models in the initial phases of neuronal research, as these are often predictive of in vivo results and are more convenient and economical than in vivo experiments at the outset of research on a given system. The properties of rho proteins and their inhibitors have not been observed to be different in vitro and in vivo in literature reports, and the results of Applicant's in vitro experiments have been confirmed in vivo." Applicants further argue with respect to the Bartsch reference that the reference evidences that typical research protocols involve in vitro experiments followed by in vivo work. Applicants argue that if in vitro work was not predictive of in vivo results, scientists would not bother to use in vitro work. Applicants further note that Bartsch's findings are not corroborated by others that report MAG inhibits axon outgrowth in vitro

and in vivo, see in particular Lehman et al., J. Neurosci., 19:7537-47, 1999.

The Strittmatter declaration notes another rho inhibitor Y-27632 that exhibits in vitro and in vivo axon regeneration. However, the Takemoto reference to which Applicant refers is a post-filing date publication and the particular teachings contained therein were not apparently known or disclosed by Applicants in instant application.

Applicants further point to a declaration and experiments conducted via Bernhard Mueller. These experiments confirm neurite outgrowth promoting effects in vivo with C2/C3 exoenzyme in a spinal cord lesion model. However, the specification as filed failed to disclose Dr. Mueller's specific teachings, and the declaration fails to disclose dates his experimentation were completed or were first publicly disclosed. While such is not required such information is relevant to the timeline of Applicants invention with respect to enablement. It is noted that a similar construct to the Mueller work was published by Barth et al., Infection and Immunity, 66(4):1364-1369, April 1998. Thus, while the declaration notes enablement of particular embodiments within the scope of the invention, the declaration does not address the full scope of the claims or speak to the predictability of extrapolating in vitro data to in vivo findings. Further the experimentation completed by Mueller was neither disclosed in instant application nor apparently known by the artisan at the time of the invention by Applicants.

Applicant's further note the post-filing date publication via McKerracher et al., and argue that the claim limitations directed to mechanical introduction, effects in spinal cord injury, white matter stroke, and traumatic brain injury support enablement by Applicant's. Applicants argue that a number of rho inhibitors are known but reference

only post-filing date publications and/or declarations.

Applicant's arguments filed 2-13-02 have been fully considered but are not persuasive. While Applicants arguments and declarations attest to the enablement of particular embodiments within the scope of Applicant's claims, the arguments and evidence are not persuasive to show that applicant's specification was enabling for the full scope of the invention as claimed, at the time of filing. The information cannot establish enablement of the invention as disclosed by the specification. The effects of alternative rho-inhibitors is not disclosed in the specification. Further, the effect of CNS axon growth in patients in vivo is not disclosed or exemplified.

As previously noted, the art evidences the unpredictability in extrapolation of data from in vitro experiments. Applicants arguments submitted 2-13-02 at pp. 1-2 also appears to recognize that the art expects and/or requires that in vitro findings be confirmed via in vivo experimentation, particularly in unpredictable arts such as in in vivo experimentation of the CNS. Further with regard to the specifics of an "effective amount", the particulars of administration and the required effects of promoting axon outgrowth in patients with spinal cord injury, white matter stroke or traumatic brain injury, the specification is required to enable the artisan to practice the invention without further undue experimentation. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The claims are drawn to a method of promoting CNS axon growth in a patient in need of axon regeneration by administering an effective amount of at least one rho protein inhibitor whereby neurite outgrowth is stimulated. To practice such a method would require a knowledge of the route, duration and quantity of administration of that rho inhibitor to a subject and this information is not provided by the instant specification. The text clearly fails to supply the guidance that would be needed by a routine practitioner because no in vivo exemplification of such method is provided. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working example, prophetic or actual, of the claimed method. In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the potential compound compositions of the instant invention and in determining a suitable route of administration. It is further noted that the only inhibitor disclosed as having activity in the specification is C. botulinum C3 exoenzyme. The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 U.S.P.Q. 150,(CCPA 1977), which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequence, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph".

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot following the guidance presented therein, practice the claimed method without first making a substantial inventive contribution. The artisan would be required to determine how to effect promotion of central nervous axon outgrowth in a patient in need thereof by administration of a suitable compound within the scope of the claims such that outgrowth is stimulated. There is no guidance on this matter within the specification as originally set forth. The artisan must choose the compound, the particular patient, the amount of selected compound, a suitable delivery method, dosage regime and duration for adequate response. These selections would only after further undue

experimentation arrive at the invention now claimed.

Thus, Applicants arguments and declarations of Dr. Strittmatter and Dr. Meuller fail to evidence enablement of the invention as filed.

Applicants argue in the amendment of 11-14-03 that the experimentation testing outgrowth was conducted on CNS myelin which is inhibitory for axon growth. Applicants allege that such testing assays are predictive or regneration after injuries because the surface mimics that confronted by axons in the CNS. Applicants allege that such data correlates to the in vivo setting and thus provides reasonable correlation to the in vivo situation in a patient as recited by the claims.

Applicants arguments filed 1-14-03 have been fully considered but are not persuasive. It is unclear to the Examiner to which data within the specification Applicants's are referring. In particular, the Examiner fails to find where in the specification the teachings with respect to experimentation on CNS myelin is disclosed. Moreover no evidence has been submitted that establishes that the artisan would consider experimentation on myelin to be either predictive of or correlating to effects seen within the adult CNS. Thus, applicants allegations are unsupported absent the submission of further facts or evidence as to guidance by the specification for experimentation with myelin and it's predictive and correlating teachings to experimentation in vivo within the CNS.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 24-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-27 depend form canceled claim 12 and thus there is insufficient antecedent basis for the claim limitations.

Priority

12. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

As previously noted the effective filing date of claims 8 and 17 drawn to a C2/C3 exoenzyme construct having the actin ADP-ribosylation activity deleted from the C2 toxin and the C3 exoenzyme activity substituted therefore, so that the construct ADP-ribosylates rho specifically and inactivates the G protein is 8-12-1998 based on a lack of support in the provisional as originally filed.

Further it is noted that instant claims 1-2, 6-13, 17 and 21-30 are drawn to administration to a patient, patients suffering from acute or chronic spinal cord injury, white matter stroke, traumatic brain injury and administration of rho inhibitors via

mechanical introduction to the axons or their non-neuronal support tissue. While the priority application appears to contemplate in vitro administration for effecting CNS axon outgrowth, the Examiner cannot find support in the provisional for the recitations as noted above directed to administration to a patient, to patients suffering from acute or chronic spinal cord injury, white matter stroke, traumatic brain injury or to patients via mechanical introduction to the axons or their non-neuronal support tissue. All experimentation is directed to the in vitro model system and no recitation of administration to a patient is found. Moreover, the provisional appears similarly limited to the effects of axon growth based solely on the rho inhibitor C3 exoenzyme Clarification of support for the scope of the claims is required for benefit of the 8-13-1997 date. Thus, the effective filing date of claims 1-2, 6-13, 17 and 21-30 is the filing date of 8-12-1998.

Claim Rejections - 35 USC § 102 or 103

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act

of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 2, 6, 12, 21-22, 25-27 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartsch et al., Neuron, 15:1375-81, 1995 or in the alternative under 35 U.S.C. 103(a) as obvious over Bartsch et al., Neuron, 15:1375-81, 1995.

Bartsch et al teach increased axonal regrowth following optic nerve crush in wild-type and MAG-deficient mice after application of the IN-1 antibody directed against the neurite growth inhibitors NI-35 and NI-250. Thus, the reference teaches the limitations of the claims with the exception that the reference is silent as to whether or not the IN-1 antibody is a compound/composition that is a rho/rac protein inhibitor. The application is silent as to how rho/rac inhibition such should be assessed. However, the Strittmatter declaration references no less than 6 different assays to determine rho inhibition including measurements of actin cytoskeleton dynamics, transcriptional regulation, cell cycle progression, programmed cell death, transformation and membrane trafficking. IN-1 is noted to exhibit neurite growth, a form of actin cytoskeleton dynamics and membrane trafficking and thus the IN-1 antibody would appear to be a rho/rac inhibitor via it's acitivities. The USPTO has insufficient resources to determine whether or not the IN-1 antibody is a compound that in fact exhibits rho/rac protein inhibition. Thus, the Examiner has insufficient facts to determine whether the Bartsch treatment is "inherently the same" or obvious since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that the IN-1 antibody is or is not a rho/rac protein inhibitor. Note the case law of In re Best 195 USPQ 430,

433 (CCPA 1977).

Applicants argue in the amendment of 11-24-03 that the amendments to the claims distinguish in that the IN1 antibody does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 11-24-03 have been fully considered but are not persuasive. Applicants allege that the mechanism whereby the IN1 antibody asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations. Note in particular that more than a single functional activity is recited. All mechanisms of the IN-1 axon outgrowth promoting effects are not disclosed. While the reference is silent as the functional mechanism whereby the IN1 antibody exerts it's effects, the mechanisms are deemed to be inherent in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the IN1 compound is not structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596

(CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings anticipate the claimed invention.

16. Claims 1, 2, 6, 12, 21-22, and 25-27 and are rejected under 35 U.S.C. 102(b) as being anticipated by Sylvain et al., Pediatric Neurology, 10(3):228-32, 1994 as evidenced via Eberlein et al., Br. J. Pharmacol., 133:1172-1180, 2001.

Lovastatin is a recognized rho inhibitor as evidenced via Eberlein et al., Br. J. Pharmacol., 133:1172-1180, 2001 as referenced within the Strittmatter declaration. Sylvain et al., teach magnetic resonance spectroscopy in Niemann-Pick disease type C: correlation with diagnosis and clinical response to cholestyramine and lovastatin. As disclosed in the abstract, "Niemann-Pick type C is an autosomal-recessive, neurovisceral storage disorder that results from defective cholesterol esterification. Cholesterol-lowering agents have been demonstrated to decrease hepatic lipids in Niemann-Pick type C patients. The objective was to determine the effects of cholesterol-lowering agents on neurologic features and to develop a noninvasive method of monitoring clinical response. A 9-month-old boy with progressive hepatosplenomegaly and neurodevelopmental delay was studied. Water-suppressed proton magnetic resonance spectra from a supraventricular volume of central white and gray matter revealed an abnormal lipid signal. The patient was treated with cholesterol-lowering agents (i.e., cholestyramine, lovastatin). Repeat standardized neurodevelopmental assessments (Peabody and Griffith scales) at 13 and 19 months were normal and magnetic resonance spectra no longer detected the previously observed lipid resonance. Early treatment of Niemann-Pick type C patients with

cholesterol-lowering agents appeared to have short-term beneficial effects. Magnetic resonance spectra provided a noninvasive means of monitoring CNS response."

Thus Niemann Pick is a neurodegenerative disease in a patient and the treatment comprises the administration of a rho inhibitor in the quantity of 0.125 mg/kg daily, gradually increased to 1.0 mg/kg b.i.d. after 8 weeks as set forth in methods, p. 229, column 2, lines 10-16. While the reference is silent as to whether or not this quantity is sufficient to stimulate neurite outgrowth it is noted that the treatment produced a beneficial response in CNS pathology as assessed via magnetic resonance spectra. Thus, the Sylvain treatment is deemed effective to block the degenerative effects of the disease and to promote neurite outgrowth. Therefore the treatment is deemed anticipatory absent convincing factual evidence to the contrary. The Nieman-Pick patient is a patient in need of axon regeneration as a result of the storage disorder. The delivery is via injection and is thus by means of mechanical introduction. Dissemination in the body via the bloodstream would effectively deliver the inhibitor to the axons or their non-neuronal support tissue.

The reference is silent as to whether or not the inhibitor is one that inhibits rac in addition to rho. Thus, the USPTO has insufficient resources to determine whether or not the lovastatin administration is sufficient to inhibit a rac protein. Thus, the Examiner has insufficient facts to determine whether the Sylvain treatment is "inherently the same" or obvious as claimed in claim 6, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior

art would neither anticipate nor render obvious the claimed invention. Specifically, that the lovastatin administration of Sylvain is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

Applicants argue in the amendment of 11-24-03 that the amendments to the claims distinguish in that the IN1 antibody does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 11-24-03 have been fully considered but are not persuasive. Applicants allege that the mechanism whereby Lovastatin asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations. All mechanisms of the Lovastatin axon outgrowth promoting effects are not disclosed. While the reference is silent as the functional mechanism whereby Lovastatin exerts it's effects, the mechanisms are deemed to be inherent in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the Lovastatin compound is not structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to

product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings anticipate the claimed invention.

17. Claims 1, 2, 6, 9, 11-12, 21-22 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Varon et al., J. of Neurotrauma 11(5):473-486, 1994 as evidenced by Takahashi et al., Biochem. & Biophys. Res. Communications, 190(3):1156-62, 1993.

Varon et al., teach two models a septo-hippocampal lesion model representing traumatic brain injury and a spinal cord sensory regeneration model representing spinal cord injury. In both models nerve growth factor administration mediates CNS axon regeneration and neurite outgrowth effects in the animal patients. However, the Varon reference is silent as to the rho/rac inhibiting properties of NGF. Takahashi et al., teaches that NGF at 50 ng/ml is effective to inhibit the ADP-robosylation of the rho protein via an indirect mechanism, see in particular abstract and results. The Takahashi reference evidences that ngf exhibits rho inhibiton and thus the molecule qualifies as a rho inhibitor. However, the references are silent as to whether or not NGF exhibits rac inhibition in addition to the rho inhibition. The USPTO has insufficient resources to determine whether or not NGF is sufficient to inhibit a rac protein. Thus, the Examiner has insufficient facts to determine whether the treatments are "inherently the same" or obvious as claimed, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that NGF is or is not a

rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

Applicants argue in the amendment of 11-24-03 that the amendments to the claims distinguish in that NGF does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 11-24-03 have been fully considered but are not persuasive. Applicants allege that the mechanism whereby NGF asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations. The Takahashi reference evidences that NGF acts as a rho inhibitor and further that at least a partial mechanism is via inhibition of the ADP-ibosylation of rho. Thus, even though all mechanisms of the NGF axon outgrowth promoting effects are not disclosed, at least one mechanism is via that claimed. While the reference is silent as to all functional mechanisms whereby NGF exerts it's effects, the mechanisms are deemed to anticipate via Takahashi and be inherent as to the other mechanisms in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the NGF compound is not structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the

same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings anticipate the claimed invention.

18. Claims 1-2, 6-7, 12-13, 21-29 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnson et al., US Patent 5,851,786 filed September 27, 1995 and issued Dec. 22, 1998.

Johnson et al., teach, "methods useful for identifying compounds capable of specifically regulating actin polymerization, stress fiber formation or focal adhesion assembly by regulating G.sub..alpha.12 and/or G.sub..alpha.13 activity in cells involved in inflammatory responses, immune responses, allergic responses and neuronal responses, kits to perform such assays and methods to control disease related to such responses," see in particular Abstract. Johnson et al., teach Example 3, regulation of Rho protein activity by G.sub..alpha.12 QL and G.sub..alpha.13 QL that is Rho-dependent. In particular Johnson discloses that Botulinum C3 Exoenzyme is an effective reagent for stimulating Rho-dependent stress fiber formation and focal adhesion assembly, see in particular Example 3A and 3B. Johnson concludes,"that G.alpha..sub.12 and G.alpha..sub.13 regulate Rho dependent actin polymerization resulting in stress fiber formation and the assembly of focal adhesions. Thus, the results clearly demonstrate that alpha..sub.12 and .alpha..sub.13 integrate heterotrimeric G protein-coupled receptors with the regulation of Rho. The results further indicate that G.sub..alpha.12 and G.sub..alpha.13 have similar ability to stimulate Rho-dependent

stress fiber formation and focal adhesion assembly. Thus, G.sub..alpha.12 and G.sub..alpha.13 can interact with a common regulator regulating Rho activation," see in particular abstract, Example 3 and columns 17-18.

Johnson et al., further teaches that such molecules are useful as therapeutic compositions for preventing and treating diseases involving abnormal growth or migration of cells and are particularly useful for preventing or treating diseases involving a neuronal response. Further Johnson teaches prevention or treatment of the neurodegenerative diseases Parkinson's disease and Alzheimer's disease, see in particular Detailed Description, paragraph 60 and claim 40. Thus, while the reference is silent as to the recitations of "promoting neurite outgrowth" and "a patient in need thereof" the reference anticipates the claimed invention because the reference teaches administration of the preferred compounds to individuals with a neurodegenerative disease, namely Alzheimer's and Parkinson's which patients are indeed "in need of axon regeneration" or "neurite outgrowth" as claimed. Johnson notes his treatment is effective and thus the amounts are deemed to provide neurite outgrowth absent convincing factual evidence to the contrary. The administraion includes via mechanical administration such as with an osmotic pump and comprises a suitable carrier, see in particular column 15.

The Johnson et al., reference is silent as to whether or not the C3 exoenzyme inhibits rac in addition to inhibiting rho. However, it is noted that C3 exoenzyme is the only molecule noted by applicants to exhibit neurite outgrowth. While the specification also does not specifiy that C3 exoenzyme inhibits rac, such is presumed by the

Examiner based upon Applicant's claim structure. Evidence to the contrary would support the enablement rejection of record with respect to a lack of enablement to the breadth of molecules encompassed by the claims. Moreover, such would appear to evidence a total lack of enablement for any such rac inhibitor as claimed. The USPTO has insufficient resources to determine whether or not the C3 exoenzyme a compound that exhibits rac protein inhibition. Thus, the Examiner has insufficient facts to determine whether the Johnson treatment is "inherently the same" or obvious since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that the C3 exoenzyme is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

Applicants argue in the amendment of 11-24-03 that the amendments to the claims distinguish in that compounds capable of regulating Gα12 and/or Gα13 do not ADP-ribosylate rho or rac, do not block the interaction between the associated kinase and either rho or rac and do not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 11-24-03 have been fully considered but are not persuasive. Applicants allege that the mechanism whereby Gα12 and/or Gα13 asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations.

All mechanisms of Gα12 and/or Gα13 axon outgrowth promoting effects are not disclosed. While the reference is silent as the functional mechanism whereby Gα12 and/or Gα13 exerts it's effects, the mechanisms are deemed to be inherent in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the Gα12 and/or Gα13 compound is not structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings anticipate the claimed invention.

19. Claims 1, 2, 6, 10, 12, 21-22 and 25-27 are rejected under 35 U.S.C. 103(a) as being obvious over Mattson et al., Stroke 1993, 24(12):I136-40; discussion I144-5, Olson et al., J. of Neurol., 1994 Dec., 242 (1Suppl. 1):S12-15 and Olson et al., Acta Neurochirurgica Supplementum, 1993, 58(3-7), Varon et al., J. of Neurotrauma 11(5):473-486, 1994 and as evidenced by Takahashi et al., Biochem. & Biophys. Res. Communications, 190(3):1156-62, 1993.

Mattson et al., teach protection of CNS neurons in culture from neuronal damage and death in a stroke model via treatment with nerve growth factor.

Mattson et al., do not teach such protection in a patient.

Olson et al., 1993 and Olson et al., 1994 teach the similarity in protection via nerve growth factor administration amongst different CNS model systems and predict its general applicability not only in the neurodegenerative diseases but for treatment of ischemia, stroke and injury, see in particular abstract.

Varon et al., further evidences the wide use and acceptance of NGF treatment in a variety of CNS diseases, specifically for the promotion of neuronal cell survival, growth and regeneration both in vitro and in vivo.

Thus, the skilled artisan would be motivated as suggested by Olson et al., 1993 and Olson et al., 1994 to treat stroke and ischemia injuries with nerve growth factor to provide for neuronal survival, neurite outgrowth and regeneration within the CNS. One of skill in the art would have expected success in such treatment based upon the success of NGF in the treatment of CNS injuries in other model systems as evidenced by Varon and the teachings of Mattson et al., that NGF is protective to CNS neurons in a culture model of CNS stroke ischemia. Thus the cumulative reference teachings render the claims obvious to the artisan.

As set forth above with respect to rac inhibition, Takahashi et al., teaches that NGF at 50 ng/ml is effective to inhibit the ADP-robosylation of the rho protein via an indirect mechanism, see in particular abstract and results. The Takahashi reference evidences that NGF exhibits rho inhibiton and thus the molecule qualifies as a rho inhibitor. However, the references are silent as to whether or not NGF exhibits rac inhibition in addition to the rho inhibition. The USPTO has insufficient resources to determine whether or not NGF is sufficient to inhibit a rac protein. Thus, the Examiner

has insufficient facts to determine whether the treatments are "inherently the same" or obvious as claimed, since the examiner cannot determine how the methods differ. Since the record does not allow the determination of if and how the claimed methods differ, the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Specifically, that NGF is or is not a rac protein inhibitor. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977). Applicants argue in the amendment of 11-24-03 that the amendments to the claims distinguish in that NGF does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 11-24-03 have been fully considered but are not persuasive. Applicants allege that the mechanism whereby NGF asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations. The Takahashi reference evidences that NGF acts as a rho inhibitor and further that at least a partial mechanism is via inhibition of the ADP-ribosylation of rho. Thus, even though all mechanisms of the NGF axon outgrowth promoting effects are not disclosed, at least one mechanism is via that claimed. While the reference is silent as to all functional mechanisms whereby NGF exerts it's effects, the mechanisms are deemed to anticipate via Takahashi and be inherent as to the other mechanisms in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the NGF compound is not

structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings anticipate the claimed invention.

20. Claims 1-2, 6-13, 17 and 21-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamata et al., Microbiol., Immunol., 38(6):421-428, 1994, Varon et al., J. of Neurotrauma 11(5):473-486, 1994, Mobley et al., 5,134,121 July 28, 1992, Mattson et al., Stroke 1993, 24(12):I136-40; discussion I144-5, Olson et al., J. of Neurol., 1994 Dec., 242 (1Suppl. 1):S12-15 and Olson et al., Acta Neurochirurgica Supplementum, 1993, 58(3-7) and Barth et al., Infection an Immunity 66(4):1364-69, April 1998.

Kamata et al., teach chick dorsal root ganglia (DRG) induced nerve outgrowth via administration of C botulinum C3 exoenzyme (ADP-ribosyltransferase) that is at least as effective as DRG outgrowth induced via the neurotropic factor NGF, see in particular abstract, Effects of C3 exoenzyme on the morphology of cultured cells, pp. 424-425 pp. 427, lines 2-23. Based on such evidence Kamata et al., conclude that C3 exoenzyme is a neurotropic agent. DRG cells contain both central and peripheral projections and thus

the outgrowth is of CNS although the outgrowth is in culture.

Kamata et al., fail to teach in vivo administration of C3 exoenzyme to promote neuronal outgrowth within the CNS in a patient.

Varon et al., teach that neurotrophic factors are well recognized for their important function on developing neurons of the PNS, to prevent or reduce degenerative responses of adult CNS to a variety of diseases and injuries, and in the regeneration of adult CNS in animals. Varon et al., further teach various model systems utilizing in vivo administration of NGF to promote neuronal outgrowth in the CNS in vivo. NGF is a molecule that has been isolated as a neurotophic factor based upon it's ability to promote neurite outgrowth in dorsal root ganglia assays.

Mobley et al., similarly teach NGF and NGF variants that are useful in the treatment of multiple neurological diseases via the mechanism of promoting neurite outgrowth, see in particular columns 6-7 and 16-18. Mobley et al., further teach that a suitable assay to screen for such molecules is via assessing the ability of a molecule to promote neuronal outgrowth in cultured dorsal root ganglia cultures, see Bioassay with dorsal root ganglia neurons, columns 19-20.

Mattson et al., teach protection of CNS neurons in culture from neuronal damage and death in a stroke model via treatment with nerve growth factor.

Olson et al., 1993 and Olson et al., 1994 teach the similarity in protection via nerve growth factor administration amongst different CNS model systems and predict its general applicability not only in the neurodegenerative diseases but for treatment of ischemia, stroke and injury, see in particular abstract.

Barth et al., teach a C2/C3 fusion protein wherein the full-length C3 ADP ribosylransferase of Clostridium limulosum is inserted to the C2IN Nterminal part that enters the cells via the binding component and thus increases the sensitivity of the target cell for C3 activity by at least several hundred fold.

Thus, Mobley et al., and Varon et al., Mattson et al., Olson et al., 1993 and Olson et al., 1994 teach the recognition in the art of neurotrophic factors to promote axon outgrowth in the CNS for a wide variety of diseases via mechanical introduction in patients. Mobley et al., further evidences that a suitable assay for predicting such effects is the dorsal root ganglia assay that was originally used in the characterization of NGF and now a multitude of known neurotrophic factors that are effective both in vitro and in vivo to promote neurite outgrowth within the PNS and the CNS in patients. Thus, one of skill in the art would have been motivated based on Kamata's teachings of C3 exoenzyme as a neurotrophic factor capable of stimulating CNS neuronal outgrowth in dorsal root ganglia cultures to use the same molecule to produces such effects in vivo in a patient in need of CNS axon outgrowth. One of skill in the art would have expected success using such a method based on C3 exoenzyme's activity in promoting CNS axon outgrowth from DRG neurons in vitro and the art's teachings of such assays in predicting utility in promoting neurite outgrowth in the CNS of patients. One of skill in the art would have been further motivated to utilize a C2/C3 fusion construct as taught by Barth et al., that provides for the same effect but with several hundred fold sensitivity as exemplified via Barth. Thus, the cumulative reference teachings render the invention obvious to the skilled artisan.

These rejections are not in conflict with the enablement rejection above. As stated in Ex parte Dash, 27 UPQ2d 1481 (BdPatApp&Int, 1993("[w]e are not unaware that we are sustaining rejections under lack of enablement based on reasons which also apply to the prior art" and "[I]f appellants overcome the lack of enablement of their claims, tey will necessarily overcome the lack of enablement of the references". All of the elements of the claimed invention were in the prior art. Further, the instant specification provides neither an element of predictability that was lacking from the prior art or the disclosure of unexpected results.

We recognize that In order for a reference to be anticipatory, it must be enabling. See In re Le Grice, 301 F. 2d 929,936, 133 USPQ 365, 371 (CCPA 1962) ("[B]efore any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in posssession of the invention."), In re Donohue, 766 F.2d 531, 533, 226 USPQ 619,621 (Fed. Cir. 1985) (reaffirming La Grice; but In re Hafner, 410F.,2d 1403, 1405, 161 USPQ 783, 785 (CCPA 1969) (finding that a disclosure that fails to teach how to use a disclosed compound, while it may serve as an anticipatory reference under 35 USC 102 may fail to support the claimed invention as required by 35 USC 112, first paragraph; In re Schoenwald, 964 F.2d 1122, 1123-24, 22 USPQ2d 1671, 1673, (Fed. Cir. 1992) (following the reasoning of In re Hafner, In re Lukach, 442 F.2d 967, 970, 169 USPQ 795, 797 (CCPA 1971) (noting that "there are...apparent anomalies between the requirements for claim-anticipating disclosures and claim-supporting disclosures"). In circumstances such as this, however, where the

specification does not appear to add anything not taught by the prior art, the examiner may not have sufficient evidence to determine which rejection is more appropriate, i.e., the art rejection or the enablement rejection. If the specification is enabling, so is the prior art reference, and vice versa.

In this regard, the statements of the Court of Claims and Patent Appeals in In re Krauch, 56 F.2d 290, 12 USPQ 257 (CCPA 1932), are enlightening. In that case, the Commissioner urged, and the CCPA agreed, that Krauch's claims were unpatentable on the basis of alternate theories. The court noted that it did not have to choose between the two alternative theories as the result was the same no matter which theory was accepted-appellants were not entitled to allowance of the appealed claims. See id. at 291-92. The reasoning of Krauch is germane to the situation where the teachings of the specification appear to be commensurate with the disclosure of a previously published reference. If the specification is enabling, so to is the reference, and the claims may be unpatentable over the teachings of that reference. If the reference is not enabling, neither is the specification, and the claims may again be unpatentable. The Examiner need not choose based on the limited evidence the rejection that is the more correct one, as the result is the same in either instance-the claims are unpatentable. It is thus proper for the Examiner to make the superficially inconsistent art and enablement rejections, and place the burden on applicant to distinguish his or her specification from the prior art and to point out how the specification goes beyond and elaborates upon what is taught by the previously published reference(s).

The instant case appears to fall squarely within the bounds of the above analysis

and thus both 35 USC 112, first paragraph and 35 USC 103 rejections are set forth herein. It is noted that Applicants traverse the enablement rejection of record, in part, by noting that "If in vitro experiments were not predictive of in vivo results, scientists wouldn't bother with in vitro work ", see also 37 CFR 1.132 declaration via Dr. Strittmatter, "My finding that rho protein inhibitors such as the C3 exoenzyme used in my application's examples promot central nervous system axon regeneration was first observed in in vitro experiment, which most investigators in the field use in initial experiments because they are predictive of in vivo physiology". Thus, it appears to be Applicant's opinion that the disclosure of the in vitro experimentation in DRG neurons is all that is required to enable the artisan to practice the claimed invention. If this is so then it also appears clear that the invention was both enabled and anticipated via Kamata et al., Microbiol., Immunol., 38(6):421-428, 1994 which teach the same CNS axon outgrowth in DRG neurons in culture via administration of C3 exoenzyme.

While it is noted that the Kamata referenceis silent as to the particulars of CNS administraion to a patient as claimed and via mechanical introduction, it is noted that each of these particulars were already of general knowledge to the artisan in the field. Such is evidenced via the disclosures of Varon, Mattson, Olson et al., 1993 and Olson et al., 1994 including administration via mechanical means, in vivo to patients with various neurological disorders including in spinal cord injury, white matter stroke and traumatic brain injury. Further the advent or a pharmaceutical composition comprising a carrier or even the particular C2/C3 construct is intrinsic. Motivation to use them are provided by the art's recognition of suitable pharmaceutical formulations to provide

increased delivery to and sensitivity of the cells. Thus, it would appear that all remaining differences betweeen the prior art disclosures and Applicant's claims are general skills known to the artisan and would be obvious therefore. Accordingly, the facts are similar to that as noted in Ex parte Dash and In re Krauch above. All of the elements of the claimed invention were in the prior art. Further, the instant specification provides neither an element of predictability that was lacking from the prior art nor the disclosure of unexpected results. If the specification is enabling, so to is the reference, and the claims may be unpatentable over the teachings of that reference. If the reference is not enabling, neither is the specification, and the claims may again be unpatentable.

Applicants argue in the amendment of 11-14-03 that their experimentation was conducted on CNS myelin which is inhibitory for axon growth. Applicants allege that such testing assays are predictive for regneration after injuries because the surface mimics that confronted by axons in the CNS. Applicants allege that such data correlates to the in vivo setting and thus provides reasonable correlation to the in vivo situation in a patient as recited by the claims. Accordingly applicants allege that their disclosure is more predictive that the prior art of in vivo CNS outgrowth. Applicants further argue as to the neurblastoma data taught by Kamata that the cells are not neurons and thus that the effects in chick ganglion would have been assumed to more likely relate to survival or differentiation or to other non-neuronal effects as opposed to axon growth. Applicants allege that Kamata does not demonstrate axon outgrowth from differentiated neurons and that it does not consider surfaces that mimic the environment

encountered in vivo after CNS damage. Applicants argue that the amendments to the claims distinguish in that NGF does not ADP-ribosylate rho or rac, does not block the interaction between the associated kinase and either rho or rac and does not physically interact with a complex comprising either rho and the associated kinase or rac and the associated kinase and thus the amendment obviates the rejection.

Applicants arguments filed 1-14-03 have been fully considered but are not persuasive. It is unclear to the Examiner to which data within the specification Applicants's are referring. In particular, the Examiner fails to find where in the specification the teachings with respect to experimentation on CNS myelin is disclosed. Moreover no evidence has been submitted that establishes that the artisan would consider experimentation on myelin to be either predictive of or correlating to effects seen within the adult CNS. Thus, applicants allegations are unsupported absent the submission of further facts or evidence as to guidance by the specification for experimentation with myelin and it's predictive and correlating teachings to experimentation in vivo within the CNS. Kamata in fact teaches axon outgrowth in differentiated neurons of chick sensory ganglion. Applicants allege that the mechanism whereby NGF asserts it's axon growth promoting function is not via the newly claimed functional activities. However, applicants have provided no facts or evidence to support such allegations. The Takahashi reference evidences that NGF acts as a rho inhibitor and further that at least a partial mechanism is via inhibition of the ADP-ibosylation of rho. Thus, even though all mechanisms of the NGF axon outgrowth promoting effects are not disclosed, at least one mechanism is via that claimed. While the reference is

silent as to all functional mechanisms whereby NGF exerts it's effects, the mechanisms are deemed to anticipate via Takahashi and be inherent as to the other mechanisms in that the end product of axon outgrowth promoting function is clearly achieved. Thus, the NGF compound is not structurally or functionally distinguished from the claims.

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). Thus, the reference teachings render the claimed invention obvious to the artisan.

Status of Claims

21. No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is ~~(703) 308-0196.~~ (571) 272-0894

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Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
February 19, 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER